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The Crystal Structure of 1,3-Bis-(8-theophylline)propane

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The crystal structure of 1,3-bis-(8-theophylline)propane (BTP, $C_{17}H_{20}N_8O_4 . H_2O$) has been determined by direct methods. BTP possesses anti-tumor activity. It crystallizes in orthorhombic space group *Pcca*; $a = 13 \cdot 28(2)$, $b = 10 \cdot 60(1)$, $c = 13 \cdot 49(1)$ Å, $Z = 4$, $D_x = 1 \cdot 44$ g.cm^{-3} and $D_m = 1 \cdot 43$ g.cm^{-3}. The integrated intensities of 1920 independent reflections wer emeasured on a diffractometer with Cu $K\alpha$ radiation. The bifunctional molecule crystallizes in a folded conformation. The propane moiety is disordered in the crystal in such a manner as to provide a statistical twofold axis of molecular symmetry utilized by the space group. While the theophylline moieties of BTP depart significantly from planarity all bond lengths and angles, with the exception of bonds C(5)–N(7) and N(7)–C(8), are within $2 \cdot 5\sigma$ of those found in theophylline itself. The water molecule occupies a position on a twofold axis and participates in a hydrogen bonding system which cross links columns of stacked BTP molecules. The hydrogen bonding network accounts for the high melting point, slight solubility and cleavage characteristics of BTP. Trial coordinates were refined by block-diagonal least-square techniques. The final *R* value was 0·059.

Introduction

Theophylline possesses no known anti-tumor activity. Of a series of bifunctional theophylline compounds connected at the C(8) position by methylene bridges of different lengths, only the 1,3-bis-(8-theophylline)-propane (BTP) has been found to possess such activity (Beech, 1963).

The distinctive activity spectrum of the bis-theophylline series (Fig. 1), indicative of the importance of the amount of separation and relative orientations of the theophylline moieties, was one reason for doing the complete crystal structure analysis of BTP. In addition, a comparison of bond lengths and angles of the theophylline moiety with those of theophylline (Sutor, 1958a) was expected to yield information concerning the effects of a substituent on the dimension of the imidazole ring. It was also hoped that complete structure analysis would delineate the relationship between the hydrogen bonding scheme, bifunctionality of the compound and the considerably higher melting point of BTP relative to theophylline,

Experimental

Synthesized according to the method of Beech (1963), BTP in powder form was generously provided by Dr
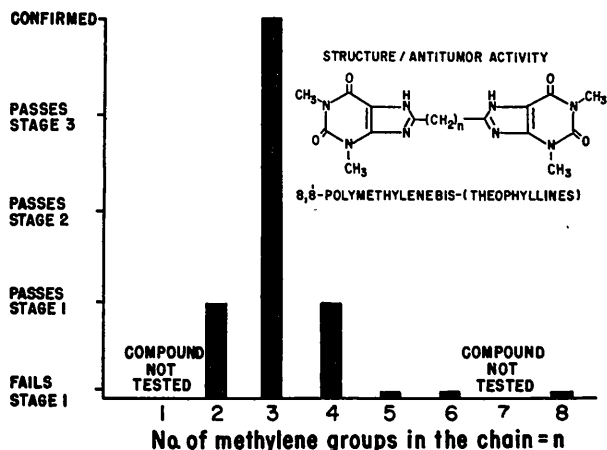

Fig. 1. Anti-tumor activity *versus* methylene chain length in the polymethylenebis-theophyllines.

Burgison of the Department of Pharmacology of the University of Maryland School of Dentistry. BTP was crystallized out of a hot ethanol/water solution (9:16). BTP crystals were found to be clear, orthorhombic prisms whose longest dimension coincided with the c axis of the unit cell.

The initial determination of space group and unit cell dimensions was made from Weissenberg rotation, zero and first level photographs were taken with a BTP crystal mounted along its c axis.

For the collection of scan data and the accurate determination of cell parameters, another crystal was mounted along its c axis on a General Electric XRD-6 spectrogoniometer with a single-crystal orienter, utilizing a scintillation counter, copper radiation source, nickel filter and pulse height analyzer. The physical constants for BTP are listed in Table 1. Density was measured by flotation in a solution of KI and water. The melting point of BTP was too high to be measured by conventional micro hot stage techniques but was higher than 350°C.

Table 1. *Physical constants for BTP crystals*

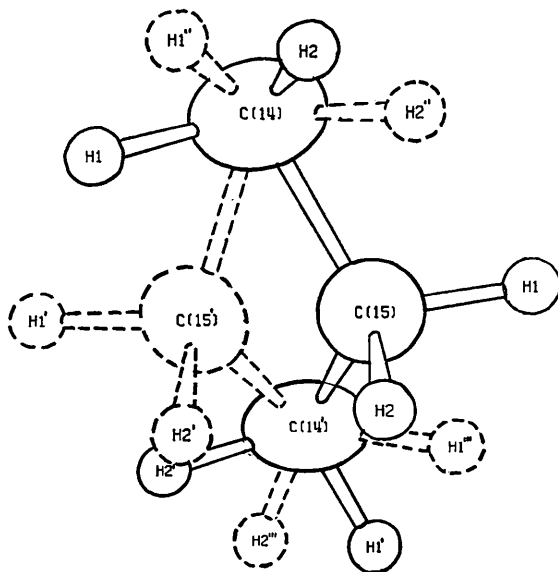|	
Molecular formula	$C_{17}H_{20}N_8O_4 . H_2O$
Molecular weight	418·23 g.mole^{-1}
Melting point	>350°C
Habit	Clear, colorless, orthorhombic prisms
Radiation	Cu $K\alpha$ (1·5418 Å)
Systematic absences	$hk0$ $h=2n+1$
	$h0l$ $l=2n+1$
	$0kl$ $l=2n+1$
Space group	$Pcca$ (no. 54); 8 general positions

Fig. 2. The disordered propane moiety of BTP. The statistical twofold axis of molecular symmetry relating the two configurations is tilted some 20° 'downward' with respect to the normal of the plane of the drawing.

Table 1 (*cont.*)

a	13·28 (2) Å
b	10·60 (1)
c	13·49 (1)
Z	4 molecules/unit cell
V	1899·0 Å^3
Observed density	1·43 g.cm^{-3}
Calculated density	1·44 g.cm^{-3}
Independent reflections	1920
Crystal size	$0·2 \times 0·2 \times 0·4$ mm along the a, b and c axes respectively
μ	9·3 cm^{-1}

A full set of data was collected manually within a sphere limited at $\sin \theta/\lambda = 0·62$. Integrated intensity data were obtained using 100 second scans of the peak positions; each scan beginning and ending 1·67° in 2θ before and after the peak. Background counts were made at each end of the scan range for 40 seconds. Their sum was multiplied by 1·25 and subtracted from the peak scan. 1920 reflections were measured in such a manner and 558 were designated unobserved using the strip chart and purely visual criteria. No corrections were made for absorption or extinction, though several low-angle reflections exhibited secondary extinction and were given zero weight during the subsequent refinement process.

During the collection of data four standard reflections were measured every three hours as a check on crystal deterioration as well as on electronic fluctuations. No decay was exhibited by these reflections, although intensities varied as much as 3 % during the two week period required to collect the data.

Lorentz–polarization corrections were applied to the intensity data. A dead time correction of 5×10^{-6} sec/count was made to reduce errors caused by coincidence.

Structure determination and refinement

Difficulty was encountered in developing a satisfactory trial model. Wilson statistics produced a scatter of points which raised doubts about the accuracy of scale and temperature factors provided by the method. A three-dimensional sharpened, point atom at rest, Patterson map proved difficult to interpret in view of the requirement that the BTP molecule utilize a twofold axis of the space group as a twofold axis of molecular symmetry. The refractory elements of the problem were not eliminated by the taking of a nuclear magnetic resonance spectrum or elemental analysis. Both techniques gave results in good agreement with the original chemical formula, even to the presence of one molecule of water of hydration per molecule of BTP, and with the valence bond scheme shown in Fig. 3.

These difficulties were surmounted and the structure readily solved by direct methods (Karle & Karle, 1963; 1966). The origin of the unit cell was specified by arbitrarily assigning positive phases to the 090, 10,4,1 and 951 reflections. The 782 and 3,8,12 were assigned sym-

bols a and b. All the operations necessary to the phase determination procedure in centrosymmetric structures were carried out by X-RAY 67 (Stewart, 1967). The four E maps resulting from all possible combinations of the signs of a and b were calculated and carefully examined. The E map calculated with the phase of 782 set positive, 3,8,12 set negative and computed from 151 terms with $|E| > 1\cdot5$ revealed all the non-hydrogen atoms of the asymmetric unit unambiguously, though several spurious peaks were present.

The coordinates of the atoms as read from the E map showed that part of the BTP molecule is disordered. Fig. 2 illustrates the nature of the disorder which is located in the methylene bridge. There are two possible conformations available to the atoms of the propane moiety. These are distributed equally among the molecules of the crystal and result in a statistical twofold axis of molecular symmetry which the individual molecule does not possess in its folded configuration.

A trial model with the population parameter of C(15) set at 0·5 produced a structure factor list which has a reliability index of 0·35 ($R=\sum||F_o|-|F_c||/\sum|F_o|$) for all observed reflections of $\sin\theta/\lambda \le 0\cdot40$. The addition of the remaining observed reflections plus five cycles of block-diagonal matrix least-squares refinement of atomic coordinates using unit weighting, reduced R to 0·23. The function minimized was $\sum w(|F_o|^2-|F_c|^2)^2$, in which $w=1$ for unit weighting and $1/\sigma(F^2)$ for final weighting. $\sigma(F^2)$ was obtained from the following relationship

$$\sigma(F^2)=\frac{1}{\text{Lp}}\,(C_t+C_b+[0\cdot05(C_t-C_b)]^2+(0\cdot05C_b)^2)^{1/2}$$

where Lp is the Lorentz–polarization correction factor, $C_t=$ total counts and $C_b=$ background counts.

At this point neither assigning anisotropic temperature factors nor switching to the final weighting scheme produced any drop in the R value. An examination of the structure factor list showed that several large, low angle reflections, expecially the 004 had observed values considerably lower (25%) than their calculated structure factors. These reflections, along with the 230 which photographs showed to have been incorrectly measured, were given zero weight in the refinement process along with all reflections coded unobserved. Ten further cycles of the least-squares refinement, utilizing anisotropic thermal parameters for non-hydrogen atoms and final weighting, reduced R to 0·092. Subsequent calculation of a difference Fourier synthesis revealed the positions of imino, methylene and methyl hydrogen atoms, though the poor resolution of the methyl hydrogen atoms may indicate some methyl group rotation. The difference map also showed a peak of sizeable electron density, located midway (2·83 Å) between two O(11) atoms of different molecules. This proved to be the oxygen of a water molecule, O(16), located on a position of twofold symmetry, an axis running in the [001] direction. The thermal motion of the water molecule was too great to allow resolution of hydrogen atoms. When O(16) along with the hydrogen atoms were included in the structure factor calculation the refinement process rapidly reduced the R value to its final value of 0·059. During the last stages of refinement the isotropic thermal parameters of two half height hydrogen atoms, C(14)H(1) and C(14)H(2″), showed a persistent tendency to converge towards doubtfully low values and were not allowed to refine any further.
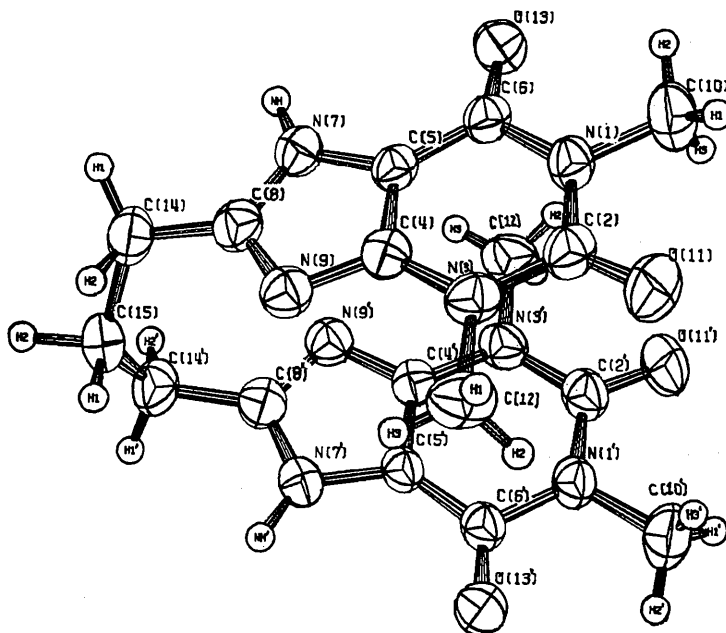

Fig. 3. The BTP molecule.

Table 2. *Final fractional atomic coordinates and multiplicities for BTP*

The coordinates listed are fractional coordinates multiplied by 10^4. Estimated standard deviations in the last significant figures are given in parentheses.

	x/a	y/b	z/c	M
N(1)	4285 (2)	2160 (2)	1010 (2)	1·000
C(2)	5325 (2)	2101 (3)	1164 (2)	1·000
N(3)	5817 (2)	3217 (2)	1309 (2)	1·000
C(4)	5292 (2)	4328 (2)	1293 (2)	1·000
C(5)	4277 (2)	4349 (2)	1132 (2)	1·000
C(6)	3701 (2)	3261 (2)	992 (2)	1·000
N(7)	4016 (2)	5607 (2)	1185 (1)	1·000
C(8)	4869 (2)	6245 (2)	1384 (2)	1·000
N(9)	5673 (1)	5495 (2)	1445 (1)	1·000
C(10)	3763 (2)	954 (3)	860 (2)	1·000
O(11)	5759 (2)	1092 (2)	1165 (2)	1·000
C(12)	6910 (2)	3221 (3)	1469 (2)	1·000

Table 2 (*cont.*)

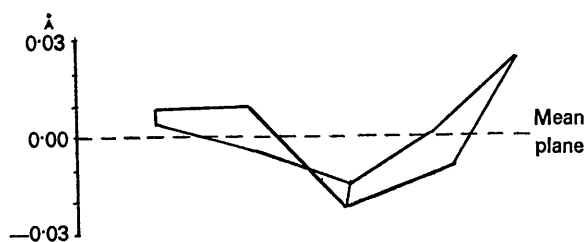|	x/a	y/b	z/c	M
O(13)	2783 (1)	3187 (2)	874 (1)	1·000
C(14)	4879 (2)	7635 (2)	1553 (2)	1·000
C(15)	4563 (4)	8047 (4)	2526 (4)	0·500
O(16)	7500 (0)	0 (0)	2010 (4)	0·488 (5)
N(7)H	3344 (18)	6013 (27)	1128 (20)	1·000
C(10)H(1)	4164 (21)	394 (26)	449 (24)	1·000
C(10)H(2)	3147 (22)	1082 (27)	492 (26)	1·000
C(10)H(3)	3553 (24)	603 (30)	1476 (23)	1·000
C(12)H(1)	7286 (26)	2966 (30)	908 (23)	1·000
C(12)H(2)	7064 (24)	2586 (28)	1976 (24)	1·000
C(12)H(3)	7180 (24)	3973 (30)	1648 (25)	1·000
C(14)H(1)	4516 (36)	8004 (45)	988 (34)	0·500
C(14)H(2)	5620 (40)	7900 (48)	1421 (37)	0·500
C(14)H(1″)	4109 (45)	7956 (52)	1632 (42)	0·500
C(14)H(2″)	5120 (35)	8027 (44)	1041 (34)	0·500
C(15)H(1)	3780 (44)	7925 (48)	2603 (39)	0·500
C(15)H(2)	4535 (32)	9092 (40)	2580 (36)	0·500

Fig. 4. Deviation from planarity of the atoms of the purine ring.

The final atomic coordinates and thermal parameters along with their corresponding standard deviations are shown in Tables 2 and 3. Table 4 lists the observed and calculated structure factors. The scattering factors used in the structure factor calculations were taken from *International Tables for X-ray crystallography* (1962). In the final cycle of refinement all shifts in parameters were found to be less than $0·2\sigma$ except for some of the anisotropic thermal parameters of O(16) which were as high as $0·5\sigma$

Table 3. *Final thermal parameters for BTP*

Estimated standard deviations are in parentheses. All anisotropic values have been multiplied by 10^5 and are defined by the expression:

$$\text{T.F.} = \exp\left[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)\right].$$

	β_{11} or β_{iso}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N(1)	529 (13)	638 (19)	558 (13)	146 (26)	62 (22)	−151 (25)
C(2)	572 (17)	790 (25)	537 (16)	284 (33)	30 (26)	−91 (32)
N(3)	438 (12)	860 (23)	515 (13)	261 (27)	10 (20)	−88 (27)
C(4)	502 (15)	712 (23)	375 (13)	59 (30)	61 (22)	−6 (28)
C(5)	495 (15)	655 (23)	403 (13)	221 (30)	−3 (22)	−63 (26)
C(6)	507 (15)	689 (22)	431 (13)	214 (31)	−8 (23)	−94 (27)
N(7)	533 (13)	674 (20)	474 (12)	168 (27)	−33 (19)	−23 (24)
C(8)	671 (18)	792 (23)	409 (15)	−13 (36)	−9 (26)	80 (30)
N(9)	512 (13)	818 (21)	475 (12)	58 (29)	−6 (21)	−16 (26)
C(10)	711 (21)	758 (27)	967 (25)	−7 (40)	115 (39)	−242 (41)
O(11)	685 (14)	856 (21)	1024 (17)	643 (27)	−88 (26)	−243 (29)
C(12)	445 (16)	1302 (36)	774 (21)	304 (40)	−62 (31)	−134 (44)
O(13)	468 (11)	895 (20)	751 (13)	148 (24)	−64 (19)	−256 (26)
C(14)	907 (23)	677 (24)	574 (17)	−100 (40)	−97 (33)	143 (32)
C(15)	580 (32)	602 (44)	630 (33)	164 (60)	106 (55)	14 (70)
O(16)	1983 (60)	3608 (109)	1384 (47)	2264 (132)	0 (0)	0 (0)
N(7)H	3·4 (0·7)					
C(10)H(1)	5·4 (0·8)					
C(10)H(2)	5·9 (0·9)					
C(10)H(3)	6·6 (0·9)					
C(12)H(1)	6·3 (0·9)					
C(12)H(2)	5·2 (0·8)					
C(12)H(3)	7·2 (1·1)					
C(14)H(1)*	2·0 (1·1)					
C(14)H(2)	2·8 (1·3)					
C(14)H(1″)	4·1 (1·5)					
C(14)H(2″)*	1·9 (1·1)					
C(15)H(1)	3·2 (1·3)					
C(15)H(2)	2·2 (1·2)					

* The thermal parameters of these atoms were fixed at these values during the final cycle of refinement.

The quantity $D = [(\sum w|F_o|^2 - |F_c|^2)^2/(n-p)]^{1/2}$, where n = number of reflections and p = the number of parameters in the least-squares refinement, was also monitored. Its final value was 1·55. During the least-squares refinement, reflections whose $w(|F_o|^2 - |F_c|^2)$ exceeded $3\,D$ were given zero weight. Reflections exceeding these limits at the end of refinement are marked with an R (Table 4).

Table 4. *Observed and calculated structure amplitudes multiplied by* 10

Observed reflections omitted from least-squares refinement are marked with an R. Those suffering from extinction with an E. Unobserved reflections are designated by asterisks.

Table 4 *(cont.)*

[Structure factor table — multiple columns of reflection indices and observed/calculated structure factors]

Table 5. *Interatomic distances and angles*

Bond		Angle	
N(1)—C(2)	1·397 (3) Å	C(2)—N(1)—C(6)	125·9 (0·5)°
N(1)—C(6)	1·402 (3)	C(2)—N(1)—C(10)	116·6 (0·4)
N(1)—C(10)	1·468 (3)	C(6)—N(1)—C(10)	117·5 (0·4)
C(2)—N(3)	1·366 (3)	N(1)—C(2)—N(3)	117·1 (0·5)
C(2)—O(11)	1·214 (3)	N(1)—C(2)—O(11)	120·6 (0·5)
N(3)—C(4)	1·368 (3)	N(3)—C(2)—O(11)	122·3 (0·5)
N(3)—C(12)	1·467 (3)	C(2)—N(3)—C(4)	119·9 (0·4)
C(4)—C(5)	1·365 (3)	C(2)—N(3)—C(12)	119·8 (0·5)
C(4)—N(9)	1·352 (3)	C(4)—N(3)—C(12)	120·3 (0·4)
C(5)—C(6)	1·396 (3)	N(3)—C(4)—C(5)	121·3 (0·5)
C(5)—N(7)	1·380 (3)	N(3)—C(4)—N(9)	126·4 (0·5)
C(6)—O(13)	1·232 (3)	C(5)—C(4)—N(9)	112·3 (0·4)
N(7)—C(8)	1·346 (3)	C(4)—C(5)—C(6)	123·3 (0·5)
C(8)—N(9)	1·334 (3)	C(4)—C(5)—N(7)	104·8 (0·4)
C(8)—C(14)	1·490 (4)*	C(6)—C(5)—N(7)	131·8 (0·5)
C(14)-C(15)	1·447 (6)*	N(1)—C(6)—C(5)	112·5 (0·4)
C(15)-C(14')	1·511 (6)*	N(1)—C(6)—O(13)	119·8 (0·4)
N(7)—N(7)H	0·99 (3)	C(5)—C(6)—O(13)	127·7 (0·5)
C(10)-C(10)H(1)	0·97 (3)	C(5)—N(7)—C(8)	106·5 (0·4)
C(10)-C(10)H(2)	0·97 (3)	N(7)—C(8)—N(9)	112·7 (0·4)
C(10)-C(10)H(3)	0·96 (3)	N(7)—C(8)—C(14)	122·3 (0·5)*
C(12)-C(12)H(1)	0·95 (3)	N(9)—C(8)—C(14)	124·9 (0·5)*
C(12)-C(12)H(2)	0·98 (3)	C(4)—N(9)—C(8)	103·7 (0·4)
C(12)-C(12)H(3)	0·90 (3)	C(8)—C(14)—C(15)	114·6 (0·6)*
C(14)-C(14)H(1)	0·98 (5)	C(14)-C(15)—C(14')	121·2 (0·8)*
C(14)-C(14)H(2)	1·03 (6)		
C(14)-C(14)H(1″)	1·08 (6)	C(5)—N(7)—N(7)H	129·7 (3·6)
C(14)-C(14)H(2″)	0·86 (5)	C(8)—N(7)—N(7)H	123·8 (3·5)
C(15)-C(15)H(1)	1·06 (6)		
C(15)-C(15)H(2)	1·11 (4)		

* Denotes bond lengths and angles affected by the disorder.

Molecular structure

The folded conformation of BTP is shown in Fig. 3. Molecular dimensions are listed in Tables 5 and 6. All dimensions are calculated from the final refined atomic coordinates. Standard deviations were calculated according to the method of Darlow (1960). Planes drawn through each theophylline moiety of the BTP molecule form a dihedral angle, defined as the acute angle formed by the normals to each plane, of 9·3°. While the deviations of individual atoms from such a plane (Table 7) are small, they are significant. Fig. 4 shows the departure from planarity of the atoms of the fused ring system.

Table 6. *Non-bonded contacts between the theophylline moieties of the BTP molecule*

	Distance
C(4)—C(4')	3·35 Å
C(4)—C(5')	3·52
C(4)—N(9')	3·53
C(5)—N(9')	3·49
C(6)—C(12')	3·52
N(7)—N(9')	3·23
C(8)—C(8')	3·03
C(8)—N(9')	3·12
C(8)—C(14')	3·17
N(9)—N(9')	3·36
C(14)–C(14')	2·58

Table 7. *Deviations of the atoms from the least-squares plane through the nine atoms of the ring system*

The atoms of the fused ring system are marked with asterisks. The equation of the least-squares plane is $2·069x + 0·888y - 13·277z = 0·2531$ Å, where x, y, z are fractions of unit-cell edges.

	Deviation
N(1)*	0·0089 Å
C(2)*	0·0048
N(3)*	−0·0041
C(4)*	−0·0154
C(5)*	−0·0213
C(6)*	0·0086
N(7)*	−0·0088
C(8)*	0·0238
N(9)*	0·0036
C(10)	0·0251
O(11)	0·0050
C(12)	−0·0195
O(13)	0·0500
C(14)	0·1216
C(15)	1·4420
N(7)H	0·0232

Until rather recently the fused ring system of purine type compounds has been treated as a planar, pseudoaromatic system. Deviations from planarity have been attributed to forces within the crystal (Macintyre, 1964). Sletten & Jensen (1969) have noted that as more accurate structural information about the purine compounds becomes available a pattern emerges in which the purine ring is bent about the C(4)–C(5) bond. The

theophylline moiety of BTP fits this pattern rather well even so far as to exhibit a slightly puckered six membered ring also found in several purine structures (Sletten & Jensen, 1969). Sutor (1958a) reported theophylline planar but the magnitude of the estimated standard deviations of atomic coordinates is large enough to obscure the size of the deviations found in later studies.

With two exceptions, bond distances and angles found in the theophylline moiety of BTP were within 2·5σ of those found in theophylline itself. At 1·380 and 1·346 Å, C(5)–N(7) and N(7)–C(8) are significantly longer than the corresponding bonds in theophylline which are 1·34 and 1·31 Å. These differences, possibly indicative of the destabilizing effect of the methylene substituent on the imidazole ring, parallel similar bond length shifts found in caffeine (Sutor, 1958b) and tetramethyluric acid (Sutor, 1963). An alternative explanation would take into account the probability of a slight disorder at the C(8) position. This would be a continuation of the disorder within the propane which in theory is present in all atoms of BTP, though its magnitude would be insignificant beyond C(8).

Bond lengths and angles within the propane moiety deviate considerably from expected values (see Table 6). A similar bridged 'sandwich compound', α-keto-1,1'-trimethylferrocene (Jones, Marsh & Richards, 1965), does not exhibit any anomalies in this region. More critical to the understanding of the BTP structure than unexpectedly short bond distances is the lack of equivalence between two chemically identical bonds, C(14)–C(15) and C(15)–C(14'), which are 1·447 and 1·511 Å respectively. The difference in bond length is greater than 10σ. The explanation lies in the nature of the disordered region. The structure was refined with two symmetry-related half-height atoms present [C(15) and C(15')]. Each atom represented a set of coordinates occupied 50% of the time by the central methylene carbon. These positions lay 1·16 Å apart and were easily resolvable by Fourier methods. It was impossible to use this half atom technique at C(14) to resolve any disorder at this position because these half atoms would have been too closely situated to permit separate resolution and refinement. The coordinates of C(14) [hence C(14')] represent a compromise between the two half-height positions and this averaging process mirrors itself in the distortion of bond lengths and angles and in the anisotropic thermal motion of C(14) which is sufficiently larger than that of the ring atoms to favor this interpretation. A difference map calculated with final refined coordinates shows slightly negative in the region of the C(14) atom.

The disorder in the bridge atoms is randomly distributed throughout the crystal, in effect creating a twofold axis of molecular symmetry which is utilized by the space group. The situation may be regarded as a form of twinning with the lattice containing those molecules of one persuasion being related to its sister lattice by a twin element (twofold axis). The two lattices

may be regarded as interpenetrating throughout the crystal and reciprocal space. If one removes the twofold axis generated by the disorder in BTP from space group *Pcca* one is left with monoclinic space group *P2/a*, *c* unique. The role played by the water of crystallization found in BTP is indicated by the fact that BTP crystallized from dimethyl sulfoxide does so in monoclinic space group *Cc*(or *C2/c*).

Molecular packing and hydrogen bonding

The folded conformation of BTP has not altered the tendency of purine type molecules to stack in columns (Sletten, Sletten & Jensen, 1969). In the BTP structure these columns run in the [001] direction, each molecule being related to its neighbor by a center of symmetry. Fig. 5 illustrates the columnar packing while the tilt of molecules in one column relative to those in the adjacent column (related by a twofold axis of symmetry) is shown in Fig. 6. Least-squares planes through symmetry related moieties in these columns form dihedral angles of 29°, while the intermolecular packing distance between theophylline moieties is 3·40 Å. The shortest intermolecular distances are listed in Table 8. Except for atoms participating in hydrogen bonds the closest molecular contacts are along the *c* axis, namely C(4)---N(7) and C(5)---N(9) which are 3·47 and 3·48 Å respectively.

Table 8. *Molecular packing*

Key to symmetry operators

1	$\frac{1}{2}-x$,	$1-y$,	$-z$
2	$\frac{3}{2}-x$,	$-y$,	z
3	$1-x$,	$-y$,	$-z$
4	$-\frac{1}{2}+x$,	$-y$,	$\frac{1}{2}-z$
5	$1-x$,	$1-y$,	$-z$
6	$\frac{3}{2}-x$,	$1-y$,	z
7	$\frac{1}{2}+x$,	y,	$-z$

(*a*) Intermolecular distances less than 3·6 Å

	Distance	Symmetry operations applied to second atom
N(7)H–O(13)	1·76 Å	1
N(7)——O(13)	2·74	1
O(11)—O(16)	2·83	2
C(4)——N(7)	3·47	3
C(10)—O(16)	3·48	4
C(5)——N(9)	3·48	5
N(9)——C(12)	3·49	6
C(10)—O(11)	3·55	3
N(3)——N(7)	3·59	6

(*b*) Methyl group packing distances less than 2·8 Å

C(12)H(1)-O(13)	2·50 Å	7
C(10)H(3)-O(16)	2·56	4
C(10)H(1)-O(13)	2·69	3
C(12)H(2)-O(16)	2·80	2

The columns of stacked molecules are cross linked by two kinds of hydrogen bonds, shown in Fig. 7. The
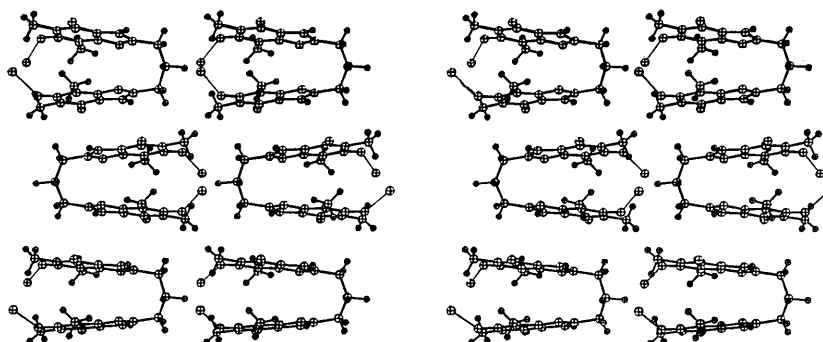

Fig. 5. Stereoscopic drawing of the packing of BTP molecules along the direction of the *c* axis.
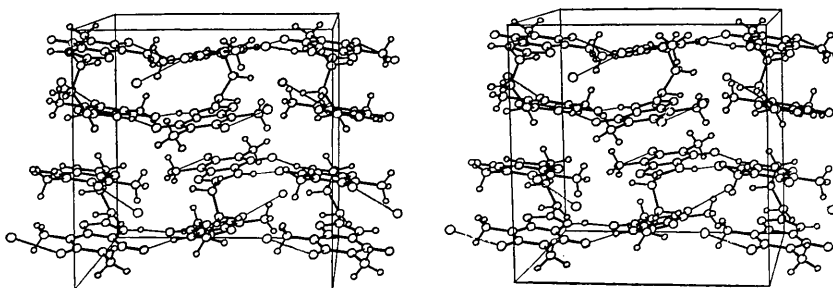

Fig. 6. Stereoscopic illustration of the contents of the unit cell. The *c* axis runs from top to bottom while the *a* axis runs the width of the drawing. The *b* axis is nearly perpendicular to the plane of the Figure.

nitrogen–oxygen pair of contacts, N(7)--O(13), are 2·74 Å long and lie approximately in the *a,b* plane of the crystal, related to one another by a twofold axis running in the [100] direction. The N(7)H---O(13) distance is 1·76 Å. The O(11)---O(16) hydrogen bond further links these columns of BTP molecules, which are themselves held together by van der Waals forces. The oxygen atom of the water molecule, O(16), is located on a twofold axis, equidistant from (2·83 Å) and hydrogen bonded to two O(11) atoms related by the same symmetry element. The water molecule is located within a cage of atoms in which the disordered C(15) atoms roughly correspond to doors at opposite ends of the cage. In occupying two positions in a completely random manner these disordered atoms provide a cage of variable length, a fact which is reflected in the large anisotropic thermal motion of the water molecule, the principal axis of which is directed from cage door to cage door. The population parameter of the O(16) atom was allowed to refine and its final value was 0·976.

There are 6 hydrogen bond contacts per BTP molecule. Theophylline crystallizes and melts in the form of hydrogen bonded dimers but the BTP molecule participates in a hydrogen bonding network which interlinks all molecules in a given layer. This is the principal reason for the high melting point of the compounds as well as for the tendency of BTP crystals to cleave perpendicular to the long axis of the crystal (a direction running from layer to layer). It also accounts for the slight solubility of BTP in any but the most polar solvents.
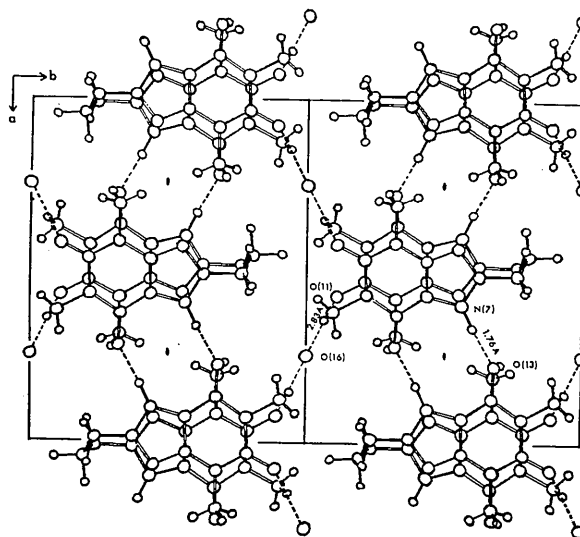
Fig. 7. The hydrogen bonding scheme in BTP. The oxygen atoms of the water molecules [O(16)] are located on twofold axis perpendicular to the plane of the drawing.

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